REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Applicant has submitted a substitute Abstract to address grammatical and/or typographical errors in the original Abstract as well as the use of "legal phraseology." The substitute Abstract contains no new matter, and Applicant has included a marked-up version showing changes made.

Applicant requests that the Title be amended as noted above to address grammatical and/or typographical errors in the original Title.

This amendment changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier for each claim. Amended claims 1, 4-11, 13-16, 19, 27, 29, 30, 43-47, and 72-88 are fully supported by the original Claims and Specification as filed. Claims 2, 3, 17, 18, 20-26, 28, 31-42, and 48-71 are requested to be canceled. After amending the claims as set forth above, claims 1, 4-16, 19, 27, 29, 30, 43-47, and 72-88 are now pending in this application.

Reasons for Applicant's Claim Amendments

In the Office Action mailed June 3, 2003, the Examiner objected to pending claims 1-16, 19, 27, 29, 30, and 43-47 for reciting subject matter that is not the subject matter of Group I, the administration of nucleic acids encoding heterologous proteins. In response, Applicant has amended claims 1, 4-16, 19, 27, 29, 30, and 43-47 to recite the administration of nucleic acids encoding heterologous proteins. Accordingly, Applicant has requested that claims 49-60 and 64-71 be canceled, because amended claims 1, 4-11, 19, 27, 29, 30, and 43-47 recite similar subject matter as canceled claims 49-60, and 64-71. Applicant has requested that claims 2 and 3 be cancelled, because they recite similar subject matter as amended claim 1. Applicant has requested that claims 20-22 and claims 61-63 be canceled to facilitate prosecution of the application. Finally, Applicant has requested that non-elected claims 17,

18, 23-26, 28, 31-42, and 48 be canceled. However, Applicant reserves the right to pursue the canceled and/or non-elected claims in one or more divisional applications.

In addition, Applicant has amended claim 4 to properly recite a Markush group. Applicant has amended claims 4-11, 13-16, 27, 30, 43-47, and 72-88 to correct grammatical and/or spelling errors and to properly recite dependent or multiple dependent claims. Applicant has amended claims 14-16 to properly recite ranges. Applicant has amended elected claim 29 to incorporate the subject matter of non-elected and canceled claim 23. Applicant has amended claims 43, 46, 47, and 72-75 to remove multiple dependencies. Finally, Applicant has amended claims 1, 4-11, 19, 27, 29, 30, 43-47, 72-79, 87, and 88 to recite "adenovirus" (*i.e.*, the elected species), to facilitate processing of the application. Applicant reserves the right to pursue the non-elected species in one or more divisional applications.

Claim Objections

In the Office Action, the Examiner objected to previously presented claims 62 and 63 as "being of improper dependent form." Applicant has canceled claims 62 and 63, obviating the Examiner's objection.

Claims Rejections – 35 U.S.C. § 112, second paragraph

In the Office Action, the Examiner maintained the rejection of claims 1-11, 27, 29, 30 and 43-47 for "indefiniteness," wherein the claims were directed to a non-elected invention. As noted above, Applicant has amended pending claims 1, 4-11, 27, 29, 30 and 43-47 to recite administration of nucleic acid encoding heterologous proteins, (*i.e.*, the subject matter of Group I as defined in the Restriction Requirement issued on December 28, 2001), and Applicant has canceled claims 2 and 3. As such, Applicant believes that the pending claims are fully compliant with 35 U.S.C. § 112, second paragraph, and Applicant respectfully requests that the Examiner reconsider the rejection.

Claims Rejections – 35 U.S.C. § 112, first paragraph

In the Office Action, the Examiner maintained the rejection of pending claims 1-16, 19-22, 27, 29, 30, 43-47, and 72-88 for "lack of enablement." Applicant has amended the claims such that none of the pending claims recite "gene therapy" or "method of therapy," and such that all of the pending claims recite the elected species (*i.e.*, "adenovirus") as the primary "agent." As such, Applicant respectfully traverses the rejection for the reasons presented in the Amendment and Reply filed on August 26, 2002, and for the following reasons.

Nature of the Invention and the Breadth of the Claims

The Examiner has stated that "[t]he nature of the invention is directed toward using the method of inhibiting the formation of neutralizing antibodies *to enhance sustained and long term expression of exogenous nucleic acids in gene therapy* of a mammal in treating a variety of disease." Office Action mailed April 24, 2002 (emphasis added). Applicant first notes that, in order to facilitate prosecution of this application, claims 20-22 and related claims 61-63, which recite "gene therapy" and/or "method of therapy," have been canceled, and all the pending claims have been amended to recite the elected species (*i.e.*, "adenovirus") as the primary "agent." As such, Applicant respectfully notes that none of the pending claims recite "to enhance sustained and long term expression" or "gene therapy," and Applicant respectfully urges the Examiner to review the recitation of the amended claims in assessing the "Nature of the Invention and the Breadth of the Claims." Under MPEP § 2164, "[t]he invention that one skilled in the art must be enabled to make and use is that *defined by the claim(s)* of the particular application or patent." MPEP § 2164 (8th ed., 2001) (emphasis added). Further, under MPEP § 2164.01, the test of enablement "requires a determination of whether th[e] disclosure, when filed, contained sufficient information regarding *the subject matter of the claims* as to enable one skilled in the pertinent art to make and use *the claimed invention*." MPEP § 2164.01 (8th ed., 2001) (emphasis added). The Applicant respectfully contends that the specification does enable one skilled in the art to make and use the subject matter as claimed.

Applicant notes that the pending claims recite methods including:

1. (Currently Amended) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising....

12. (Previously Presented) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising....

19. (Currently Amended) A method for reducing an anti-heterologous protein immune response in a mammal, including human, subject to the administration of said nucleic acid sequence encoding said heterologous protein, said method comprising....

27. (Currently Amended) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein, said method comprising....

29. (Currently Amended) A method for therapy of a mammal affected by a disease wherein at least one endogenous protein is involved in said disease etiology, said method comprising inhibiting the biological functions of said endogenous protein by enhancing the production of neutralizing antibodies against said protein by:....

80. (Currently Amended) A method of inhibiting in a mouse formation of neutralizing antibodies directed against a heterologous protein, said method comprising....

Again, Applicant respectfully contends that one skilled in the art, based on the specification as filed, could practice the steps recited in these claims without undue or unreasonable experimentation. As such, Applicant respectfully contends that these claims, as well as the additional claims in the application, are fully enabled.

For example, amended claim 1 fully recites:

1. (Currently Amended) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising:

co-administering to said mammal, an adenovirus in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and a nucleic acid sequence encoding said heterologous protein, said adenovirus being administered prior to or simultaneously with said nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

Applicant respectfully contends, based on the specification, that one skilled in the art would not have to undertake undue or unreasonable experimentation to "co-administer[] to [a] mammal, an adenovirus in an amount sufficient to deplete or inhibit at least some antigen presented cells of [the] mammal," and to co-administer "a nucleic acid sequence encoding a heterologous protein," wherein the adenovirus can be "administered prior to or simultaneously with [the] nucleic acid," to "inhibit[] the production of neutralizing antibodies against [the] protein." Similarly, based on the specification, Applicant respectfully contends that one skilled in the art would not have to undertake undue or unreasonable experimentation to practice any of the methods recited in the pending claims. Applicant respectfully urge the Examiner to reconsider the "Nature of the Invention and the Breadth of the Claims" based on the recited subject matter of the amended claims.

State of the Art

The Examiner has stated that "[a]t the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid/liposome complexes, was considered to be highly unpredictable." Office Action mailed April 24, 2002. Quoting Verma *et al.*, (1997) Science, Vol. 389, page 239, column 3, paragraph 2, the Examiner stated, "'[t]he Achilles heel of gene therapy is gene delivery' [and] 'most of the approaches suffer from poor efficiency of delivery and transient expression of the gene.'" *Id.* Further, quoting Marshall, (1995) Science, Vol. 269, page 1054, column 3, paragraph 2 and page 1055, column 1, the Examiner stated that "'difficulties in

getting genes transferred efficiently to target cells-and getting them expressed- remain a nagging problem for the entire field.'" *Id.* In emphasizing the importance of "sustained levels of therapeutically effective protein expression," the Examiner again quotes Verma *et al.*, stating that "'...the search for such combinations is a case of trial and error for a given type of cell.'" (*Id.* quoting Verma *et al.*, *supra*, page 240, bridging sentence of columns 2-3). The Examiner also contends that "[t]he state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result," (*Id.* citing Ross *et al.*, Human Gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Regarding immunization, the Examiner states that "'[t]he principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated,'" (*Id.* quoting Ertl *et al.*, (1996) Viral Immunology, Vol. 9(1), page 2, lines 32-35). The Examiner concludes, "[t]hus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low." *Id.*

Applicant addresses each of the Examiner's arguments regarding the "State of the Art" in turn below. However, Applicant first notes that, in order to facilitate prosecution of this application, claims 20-22 and related claims 61-63, which recite "gene therapy" and/or "method of therapy," have been canceled, and all the pending claims have been amended to recite the elected species (*i.e.*, "adenovirus") as the primary "agent." Further, Applicant notes that all of the cited references were published more than four years prior to the date of filing of the instant application, and as such, the authors of the cited reference may not present an accurate opinion of the state of the art at the time the instant application was filed.

(I) "[a]t the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid/liposome complexes, was considered to be highly unpredictable."

Applicant first notes that none of the pending claims recite "gene therapy." Rather, for example, claim 1 recites "co-administering to said mammal, an adenovirus in an amount

sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and a nucleic acid sequence encoding said heterologous protein, said adenovirus being administered prior to or simultaneously with said nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against said heterologous protein." Applicant respectfully contends that the "State of the Art" of administering agents to inhibit the production of neutralizing antibodies against a heterologous protein was not unpredicatable at the time of filing. The phenomenon of "tolerance" is long recognized in the field of immunology, and immunologists have achieved "tolerance" using various experimental models. *See* Tizard, Immunology: An Introduction, p. 264-270 (1988).

(II) "'[t]he Achilles heel of gene therapy is gene delivery' [and] 'most of the approaches suffer from poor efficiency of delivery and transient expression of the gene.'"

Applicant respectfully notes that the claimed methods do not recite "gene therapy" nor do the claims recite non-transient expression (*i.e.*, "sustained expression"). As such, Applicant respectfully requests that the Examiner reconsider the "State of the Art" in regard to the subject matter recited in the claims.

(III) "'difficulties in getting genes transferred efficiently to target cells-and getting them expressed- remain a nagging problem for the entire field.'"

Applicant respectfully notes that none of the instant claims recite "transferring genes *efficiently to target cells*" or "expressing the gene *in the target cell*" (emphasis added). Rather, as noted above for claim 1, the method includes administering "an adenovirus in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal...thereby inhibiting the production of neutralizing antibodies against said heterologous protein." As such, the putative problem in the field of *gene therapy* of "transferring genes *efficiently to target cells*" or "expressing the gene *in the target cell*" would not require one skilled in the art to undertake undue or unreasonable experimentation to practice the subject matter recited in the claims.

(IV) "sustained levels of therapeutically effective protein expression,"

Again, Applicant respectfully notes that the instant claims do not recite "sustained levels." While "sustained levels" of protein expression may be goal for "gene therapy" and while the threshold of demonstrating "sustained levels" of protein expression may be high in some instances, the instant claims do not recite "sustained levels." As such, Applicant respectfully requests that the Examiner reconsider the proper "State of the Art" in regard to the claimed subject matter.

(V) "'...the search for such combinations [of sustained protein expression] is a case of trial and error for a given type of cell.'"

As noted, Applicant respectfully notes that the claimed methods do not recite "sustained protein expression in a particular type of cell," and Applicant respectfully requests that the Examiner reconsider the "State of the Art" in regard to the subject matter as claimed.

(VI) "[t]he state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result"

Again, Applicant respectfully notes that the instant claims do not recite "therapeutically effective protein expression." To demonstrate "therapeutically effective protein expression," scientists and/or physicians typically require that an expressed protein, (*e.g.*, an enzyme), can be shown to functionally replace a defective version in a patient. While the threshold of enablement for demonstrating "therapeutically effective protein expression" may be high, the instant claims do not recite "therapeutically effective protein expression." As such, Applicant respectfully requests that the Examiner reconsider the proper "State of the Art" in regard to the claimed subject matter.

(VII) "'[t]he principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated,'"

Applicant notes that the instant claims do not recite "genetic immunization." Further, although Applicant has elected "adenovirus" in response to an election of species requirement issued by the Examiner, Applicant notes that there were many viral expression systems that

had been developed and successfully used to elicit immune responses at the time of filing of the instant application. For example, see Lindsay *et al.*, *J. Immunol.* 2001 Jun 15;166(12):7625-33 (discussing the use of recombinant adenoviral vector to express IL-10 and to induce remission of colitis in afflicted mice); Balasuriya *et al.*, *J. Virol.* 2000 Nov;74(22):10623-30 (discussing the use of Venezuelan equine encephalitis virus vectors to express heterologous proteins in mice and to induce neutralizing antibodies); Rose *et al.*, *J. Virol.* 2000 Dec;74(23):10903-10 (discussing the use of recombinant vesicular stomatitis virus vectors to express heterologous proteins in mice and to induce neutralizing antibodies); Mandl *et al.*, *J. Virol.* 2001 Jan;75(2):622-7 (discussing the use of recombinant poliovirus vectors to express heterologous proteins in mice and to induce neutralizing antibodies); Weidinger *et al.*, *Vaccine* 2001 Apr 6;19(20-22):2764-8 (discussing the use of modified vaccinia virus Ankara vectors to express heterologous proteins in rats and to induce an antibody response); Belshe *et al.*, *J. Infect. Dis.* 2001 May 1;183(9):1343-52 (discussing the use of canary pox vectors to express heterologous proteins in humans and to induce neutralizing antibodies); Phenix *et al.*, *Vaccine* 2001 Apr 30;19(23-24):3116-23 (discussing the use of Semliki Forest virus vectors to express heterologous proteins in chicks and to induce an antibody response); and Nilsson *et al.*, *Vaccine* 2001 May 14;19(25-26):3526-36. (discussing the use of Semliki Forest virus vectors to express heterologous proteins in monkeys and to induce an antibody response).

Notably, all these articles were published before the time of filing of the instant application, and they provide *only a small random sample* of the art that had been published on the use of viral vectors to express heterologous proteins *in vivo* to induce an immune response. As such, even if a particular protein may demonstrate an anomalous intransigence in regard to obtaining a suitable viral vector for its expression, there are many systems to try, and it would not entail undue or unreasonable experimentation to obtain a viral vector that expresses the protein. Most viral vectors systems only require that the corresponding gene be cloned into the viral vector, which has been a routine practice in the art of molecular biology for many years. In addition, Applicant respectfully contends that there were many non-viral expression systems that had been developed and successfully used to elicit immune responses at the time of filing of the instant application, (*e.g.*, bacteria, naked DNA, *etc.*). As such,

Applicant requests that the Examiner reconsider the "State of the Art" in regard to the subject matter as claimed.

Reviewing the factors listed in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), Applicant respectfully contends that the subject matter recited in the pending claims is fully enabled under 35 U.S.C. § 112, first paragraph:

First, (A) "The breadth of the claims": The claims recite "adenovirus" as an agent, and while the claims encompass an unlimited number of proteins, as noted above, many different proteins have been expressed in many different vector systems, and it would not have entailed undue or unreasonable experimentation to obtain a suitable expression system for a given protein at the time the instant application was filed;

(B) "The nature of the invention": As noted above, the nature of the claimed subject matter relates to "co-administering to [a] mammal, an adenovirus in an amount sufficient to deplete or inhibit at least some antigen presenting cells of [the] mammal, and a nucleic acid sequence encoding [the] heterologous protein, [the] adenovirus being administered prior to or simultaneously with [the] nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against [the] heterologous protein," (*e.g.*, as recited in claim 1);

(C) "The state of the prior art": As noted above, the state of the prior art of inducing "tolerance" was highly advance at the time of filing, and the state of the prior art of recombinant protein expression to achieve an immune response *in vivo* was highly advanced at the time of filing, with many vectors and systems having been developed and tested in a variety of animals;

(D) "The level of one of ordinary skill": The level of skill for an ordinary immunologist or molecular biologist was arguably very high at the time of filing;

(E) "The level of predictability in the art": The level of predictability in the art of inducing "tolerance" was very high at the time of filing. Likewise, the level of predictability of recombinant protein expression to achieve an immune response *in vivo* was very high at the time of filing—a molecular biologist would have had a reasonable expectation of success

that a given protein, cloned into a given system, would be expressed *in vivo* when introduced into an animal, even if the expression might only be transient, and that the protein would elicit an immune response;

(F) "The amount of direction provided by the inventor": The specification provides a detailed, working example, and as previously noted, "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors." MPEP § 2164.02;

(G) "The existence of working examples": As noted, Applicant provides a working example; and

(H) "The quantity of experimentation needed to make or use the invention based on the content of the disclosure": Applicant respectfully contends that, based on the content of the disclosure and what is generally known in the art, it would not have required undue or unreasonable experimentation to practice the subject matter as claimed at the time the application was filed. Considering all these factors together, Applicant believes that the claimed subject matter is fully enabled, and Applicant respectfully requests that the Examiner reconsider the rejection under 35 U.S.C. § 112, first paragraph.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 09/03/03

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MARKED UP VERSION SHOWING CHANGES MADE

ABSTRACT

~~The invention relates to~~ Disclosed is a method of modulating neutralizing antibodies formation against ~~an~~ a heterologous protein. The ~~invention also relates to the use of such~~ method may be used to induce ~~tolerisation~~ tolerance of the immune system towards ~~said~~ the protein, such ~~tolerisation~~ tolerance being useful to allow long-term gene therapy or transgene expression. The ~~invention also relates to the use of a~~ method ~~of the invention~~ may also be used to provide an animal with a reproducible functional inactivation phenotype of an endogenous protein of the animal.